

# Endocrinologic and Metabolic Drugs Advisory Committee Meeting

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## Saxagliptin BMS-477118

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1 April 2009



Bristol-Myers Squibb

AstraZeneca 

# Introduction

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Joseph Lamendola, PhD

BMS, Vice President,  
Global Regulatory Sciences

# Saxagliptin FDA Advisory Committee Agenda

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| Introduction .....                         | Joseph Lamendola, PhD<br>BMS, Vice President,<br>Global Regulatory Sciences              |
| Overview of Development Program .....      | Robert Wolf, MD, FACC<br>BMS, Vice President,<br>Development Lead, Saxagliptin           |
| Clinical Efficacy .....                    | Roland Chen, MD<br>BMS, Group Director,<br>Cardiovascular / Metabolics                   |
| Clinical Safety .....                      | Roland Chen, MD  |
| Cardiovascular Safety .....                | Robert Wolf, MD, FACC  |
| Assessment of Benefit-Risk .....           | Robert Wolf, MD, FACC  |
| Assessment of Saxagliptin Post-approval .. | Brian Daniels, MD<br>BMS, Senior Vice President,<br>Global Development & Medical Affairs |

# Consultants Available to the Committee

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## **John Alexander, MD, MHS, FACC**

Associate Professor of Medicine  
Division of Cardiovascular Medicine  
Duke University Medical Center

## **Mark Gorrell, BSc, PhD**

Associate Professor  
Centenary Institute of Cancer Medicine & Cell Biology  
Faculty of Medicine  
University of Sydney

## **Princy Kumar, MD**

Professor of Medicine and Microbiology  
Chief, Division of Infectious Diseases  
Georgetown University School of Medicine

## **Brian Strom, MD, MPH**

George S. Pepper Professor of Public Health and Preventive Medicine in  
Biostatistics and Epidemiology  
University of Pennsylvania School of Medicine

# Saxagliptin Development Program

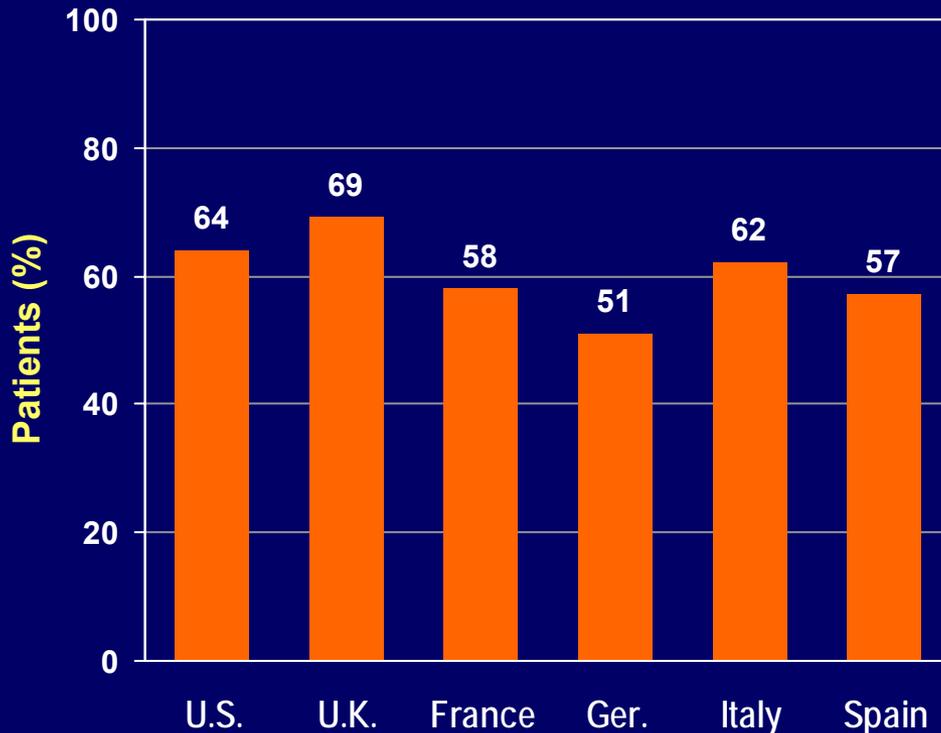
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Robert Wolf, MD, FACC

BMS, Vice President,  
Development Lead, Saxagliptin

# Patients Often Not at Goal and Suffer Many Safety / Tolerability Issues

Percentage of patients not controlled  
(relative to A1C Target of 7.0%)



## Drawbacks of Key Classes

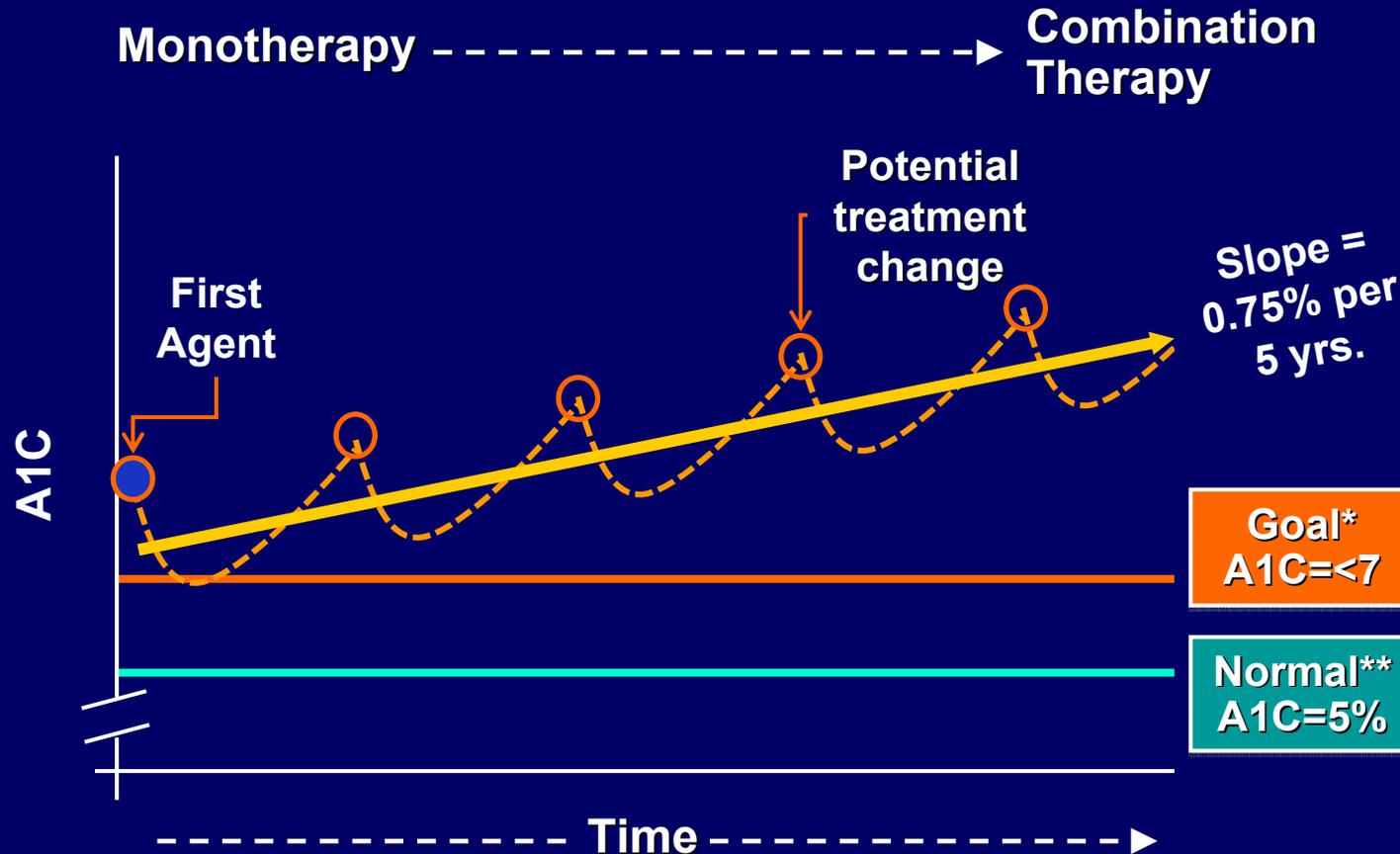
- ◆ **Metformin**
  - GI Effects
- ◆ **Sulfonylureas**
  - Weight Gain
  - Hypoglycemia
  - Cardiac Effects
- ◆ **TZDs**
  - Weight Gain
  - Edema
  - **CHF Contra-Indication**

Note: U.S. and EU percentage come from different studies and thus may not be entirely consistent —  
EU data from physician chart review; U.S. data from NHANES 1999-2000

Source: BMS Market Research; BMS Outcomes Research

# The Progressive Nature of Type 2 Diabetes Ultimately Overwhelms Medications

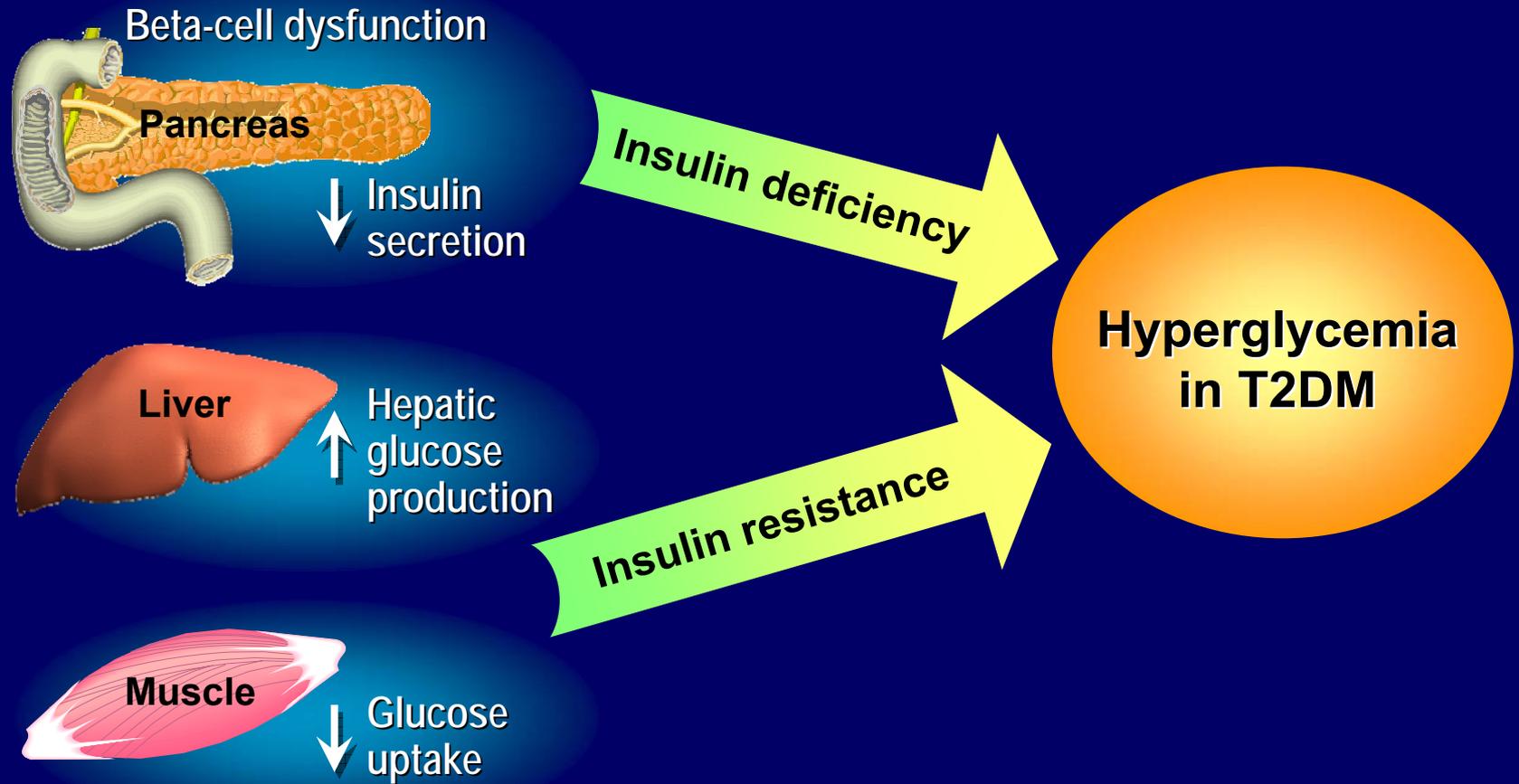
## Glycemic Control in an Illustrative Patient



Sources: ADOPT, UKPDS

(\* According to the ADA; (\*\* according to the NIH)

# Pathophysiology of Type 2 Diabetes Mellitus (T2DM)



# “Incretin Effect” Important to Post-Prandial Insulin Secretion

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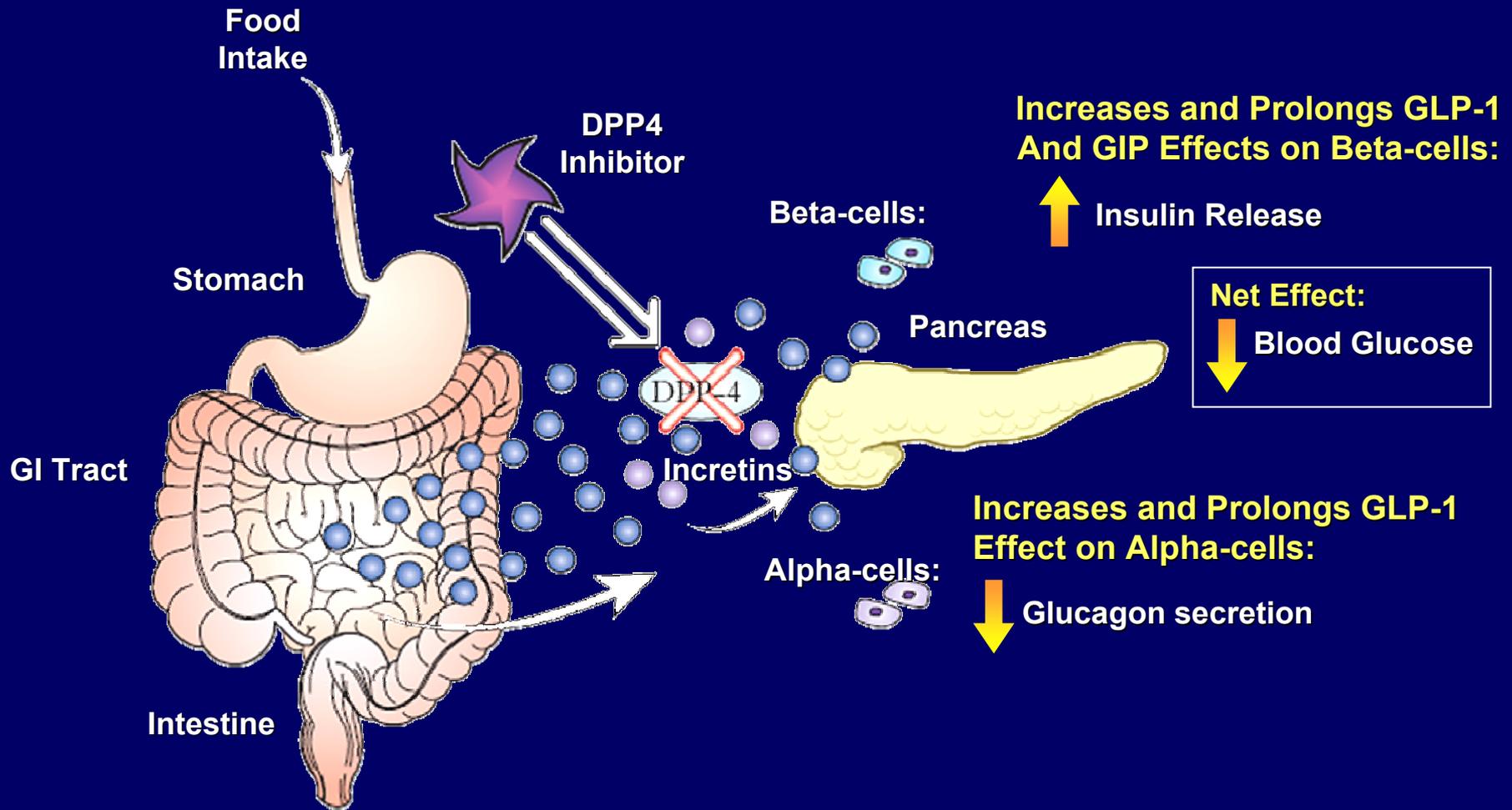
Insulin response enhanced by 70% for oral versus IV route of administration of glucose<sup>1</sup>

“Incretin Effect” mediated primarily by release of two peptide hormones from gut after oral caloric intake<sup>2</sup>

- ◆ GLP-1 (Glucagon-like Peptide-1)
- ◆ GIP (Glucose-dependent Insulinotropic Polypeptide)

**Rapidly inactivated by cleavage of N-terminal dipeptide by DPP4**

# How DPP4 Inhibitors Work

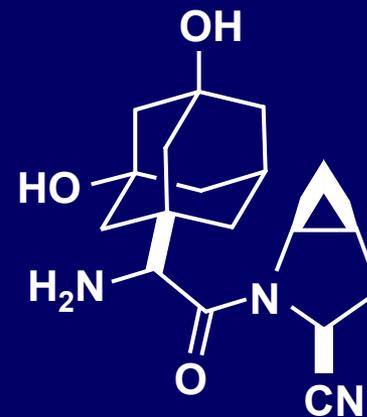


# Properties of Saxagliptin

- ◆ Highly potent, competitive inhibitor of DPP4
- ◆ 2 orders of magnitude or greater selectivity for DPP4 versus other proteases
- ◆ Major active mono-hydroxy metabolite (BMS-510849) is 2-fold less potent than saxagliptin
- ◆ Pharmacodynamic properties of 5 mg dose consistent with once-daily dosing
- ◆ Rapidly and extensively absorbed after oral dosing; may be taken without regard to meals
- ◆ Predictable and dose-proportional pharmacokinetics similar in healthy and diabetic patients with minimal accumulation with once-daily dosing
- ◆ Clearance of saxagliptin and/or its metabolites via metabolism, renal, and non-renal routes



**BMS-477118**



**BMS-510849**

# Saxagliptin Development Program

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## Non-clinical Development (*in vitro* / *in vivo*)

- ◆ Pharmacodynamics
- ◆ Safety Pharmacology
- ◆ Pharmacokinetics
- ◆ Drug Metabolism
- ◆ Toxicology / Toxicokinetics

## Clinical Development

- ◆ Clinical Pharmacology Studies
  - Safety / Pharmacokinetics / Mechanism of Action
  - Drug-drug Interactions
  - Special Populations
- ◆ Phase 2b / 3
  - Dose-ranging
  - Safety / Efficacy

# Saxagliptin – Proposed Indications

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## Indications

- ◆ Saxagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes

## Treatment Settings

- ◆ Monotherapy
- ◆ Add-on combination to MET, SU, TZD
- ◆ Initial Combination with MET

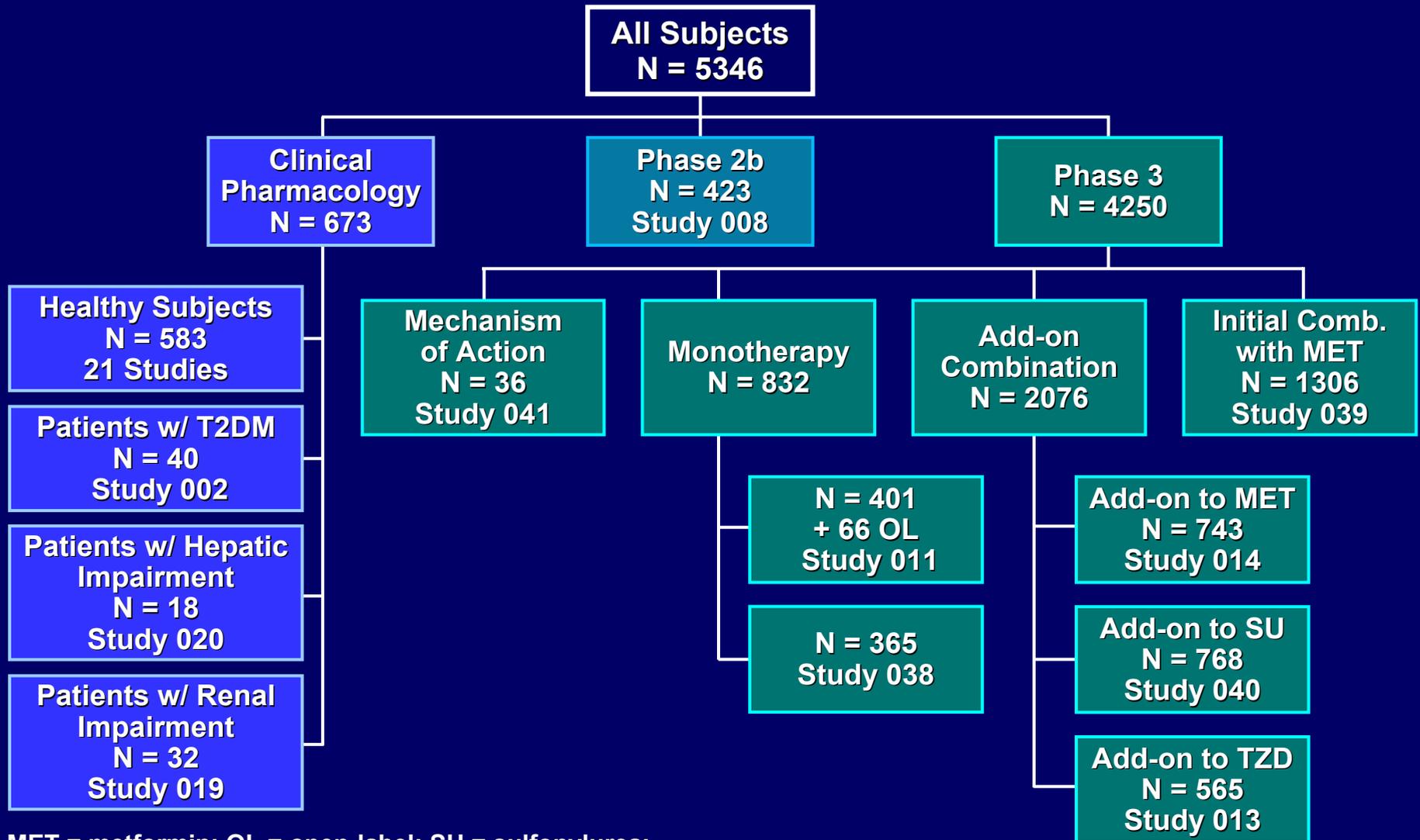
# Saxagliptin Clinical Program

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Roland Chen, MD

BMS, Group Director,  
Cardiovascular / Metabolics

# Saxagliptin Clinical Development Program



MET = metformin; OL = open-label; SU = sulfonyleurea;  
T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione

# Clinical Pharmacology Program: Key Findings

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- ◆ **Saxagliptin administered once daily was generally safe and well-tolerated up to doses of up to 80 times the proposed usual dose (400 mg once daily for 2 weeks)**
- ◆ **No signal for QTc prolongation or heart rate changes in a thorough QTc study**
- ◆ **Based on adverse events, safety signals were not identified for hypoglycemia, localized edema, or skin lesions**
- ◆ **Based on laboratory blood tests, hepatic, striated muscle, and renal safety signals were not identified**

# Clinical Pharmacology Program: Key Findings

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- ◆ **No clinically important PK differences (< 2-fold differences in exposure) in adults on the basis of age, gender, weight, hepatic impairment, or mild renal impairment**
- ◆ **Higher exposures in moderate or severe renal impairment is manageable via a dose adjustment to one-half the usual dose (2.5 mg QD)**
- ◆ **Low potential for pharmacokinetic drug-drug interactions with medications commonly used by T2DM patients**

# Saxagliptin Clinical Efficacy

# Summary of Phase 2b/3 Clinical Program

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## 8 Phase 2b / 3 Clinical Studies

- ◆ 4673 subjects, 3422 saxagliptin treated
- ◆ Phase 2b, monotherapy dose-ranging study
- ◆ Six pivotal phase 3 studies
  - Two monotherapy
  - Three add-on combination
    - MET
    - TZD
    - SU
  - One initial combination with metformin
- ◆ Phase 3 mechanism of action study

# Phase 2b Dose-Ranging Study

## Dose Selection for Phase 3

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### Phase 2b Study

- ◆ Saxagliptin 2.5–40 mg once daily versus placebo for 12 weeks
- ◆ Maximal A1C / glucose lowering at 5 mg without incremental benefit at higher doses
- ◆ No dose-limiting toxicity

### Dose Selection for Phase 3

- ◆ 5 mg dose included in all studies in the Phase 3 program
  - 2.5 mg enabled exploration of lower-end of dose range
  - 10 mg provided additional safety experience at high-end of dose range and addressed whether greater efficacy would be seen with longer exposure

# Key Enrollment Criteria – Pivotal Phase 3 Studies

## Inclusion Criteria

- ◆ **A1C:**
  - Monotherapy / Add-on MET** 7 – 10%
  - Add-on TZD** 7 – 10.5%
  - Add-on SU** 7.5 – 10%
  - Initial combination** 8 – 12%
- ◆ **Men and Women, 18 – 77 years**

## Exclusion Criteria

- ◆ **Significant CV event within 6 months**
- ◆ **CHF (NYHA Class III and IV or LVEF  $\leq$  40%)**
- ◆ **Immunocompromised status**
- ◆ **Abnormalities on screening tests of hepatic, renal and hematological function**

# Study Designs – Pivotal Phase 3 Studies

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- ◆ Six randomized, double-blind, controlled, parallel arm, multi-center studies
- ◆ Placebo lead-in period
- ◆ 24-week short-term period
- ◆ Controlled long-term extensions blinded to site and subject (12–42 months)
- ◆ Provision for rescue medication / discontinuation based on pre-specified glycemic criteria
  - Metformin (4 studies) or pioglitazone (2 studies) provided as rescue therapy

# Primary and Common Secondary Endpoints Pivotal Phase 3 Studies

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## Primary Endpoint

- ◆ **Change in A1C from baseline to Week 24 of double-blind treatment**

## Secondary Endpoints

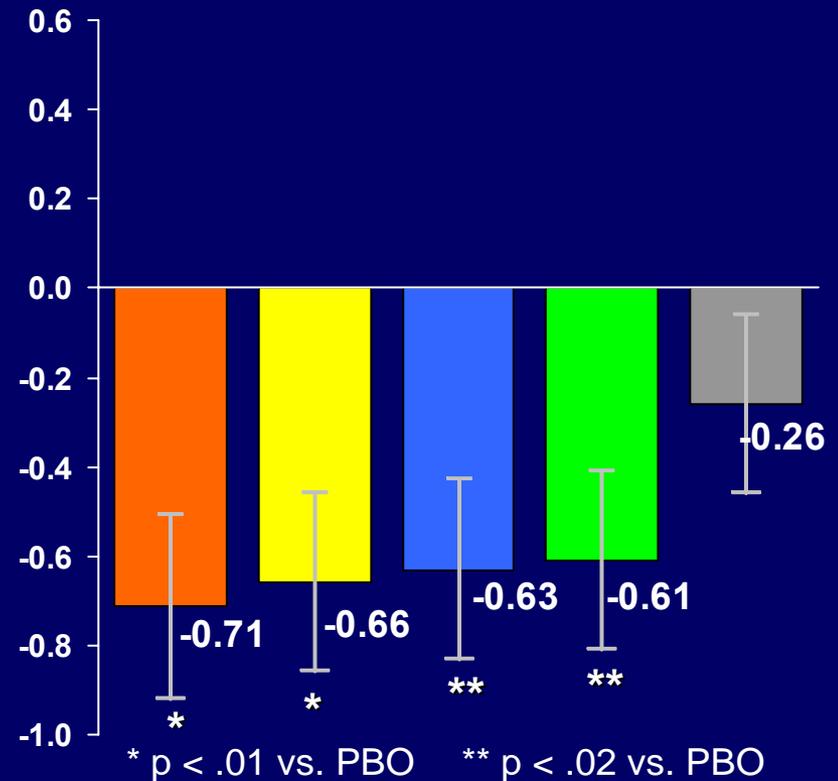
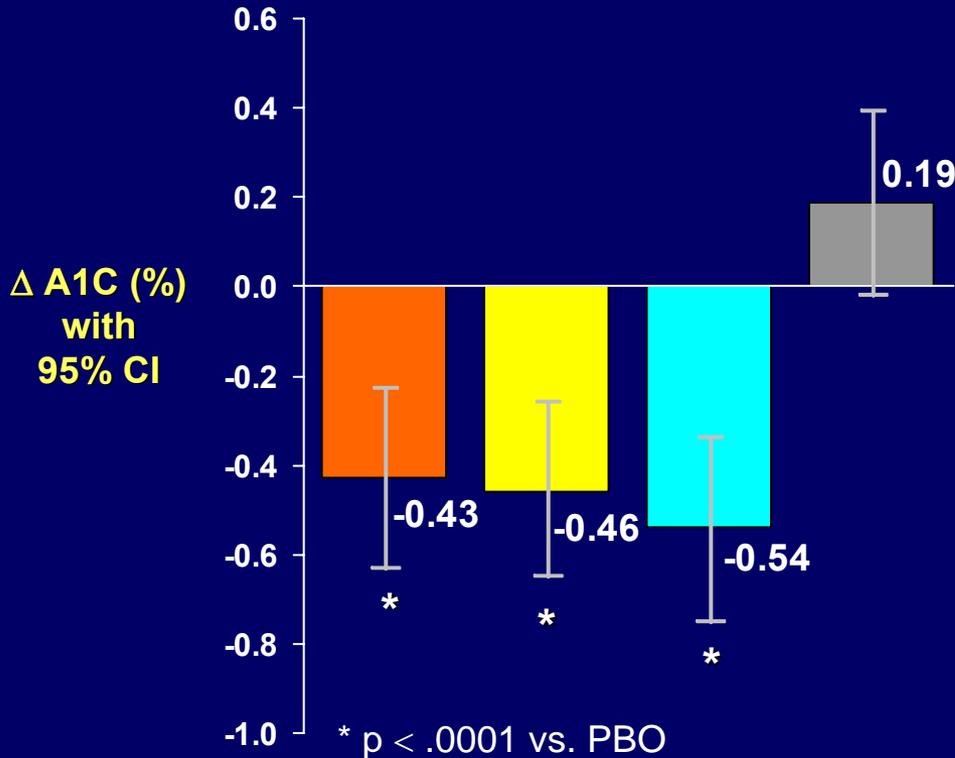
- ◆ **Change from baseline to Week 24 in fasting plasma glucose**
- ◆ **Proportion of patients achieving a therapeutic glyceemic response defined as A1C < 7% at Week 24**
- ◆ **Change from baseline to Week 24 in the area under the curve from 0 to 180 minutes for postprandial glucose response to an oral glucose tolerance test**

**Efficacy endpoints evaluated prior to initiation of rescue therapy**

# Change from Baseline in A1C at Week 24 (LOCF)

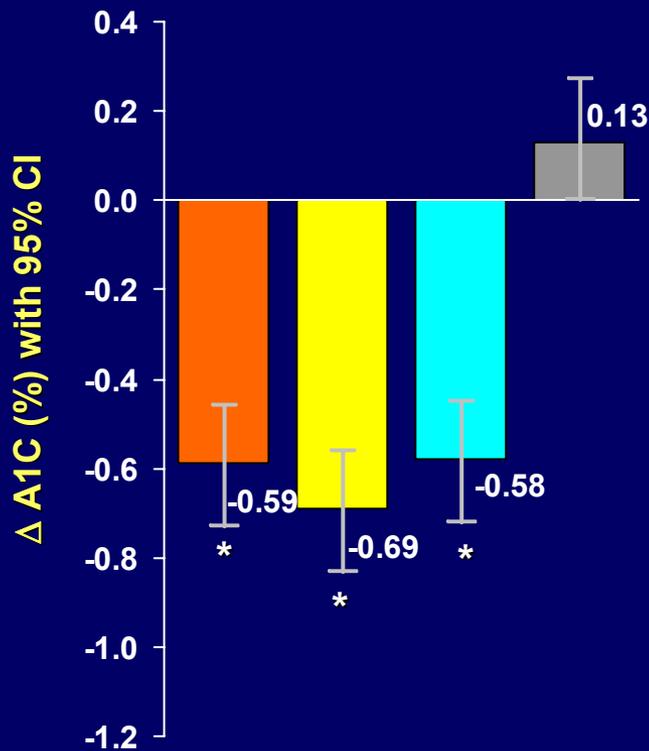
| Dose         | SAXA (mg) |      |      | PBO  |
|--------------|-----------|------|------|------|
|              | 2.5       | 5    | 10   |      |
| n =          | 100       | 103  | 95   | 92   |
| Bsl Mean (%) | 7.91      | 7.98 | 7.85 | 7.88 |

| SAXA (mg)    | SAXA (mg) |       |             |       | PBO  |
|--------------|-----------|-------|-------------|-------|------|
|              | QAM 2.5   | QAM 5 | QAM 2.5 / 5 | QPM 5 |      |
| n =          | 67        | 69    | 69          | 70    | 68   |
| Bsl Mean (%) | 8.04      | 7.93  | 8.02        | 7.88  | 7.79 |

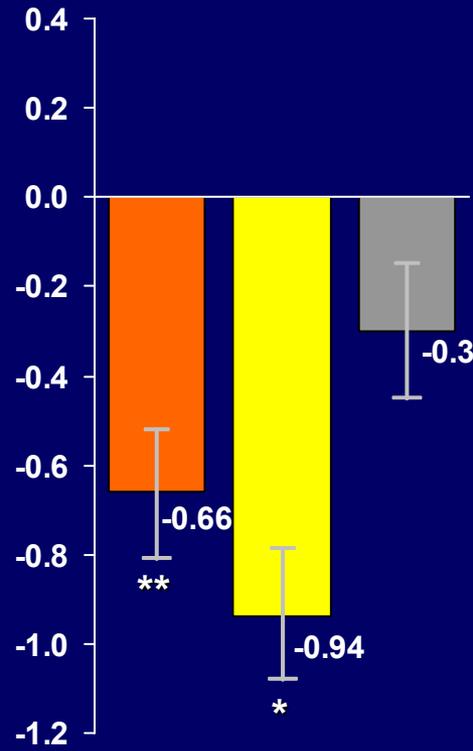


# Change from Baseline in A1C at Week 24 (LOCF)

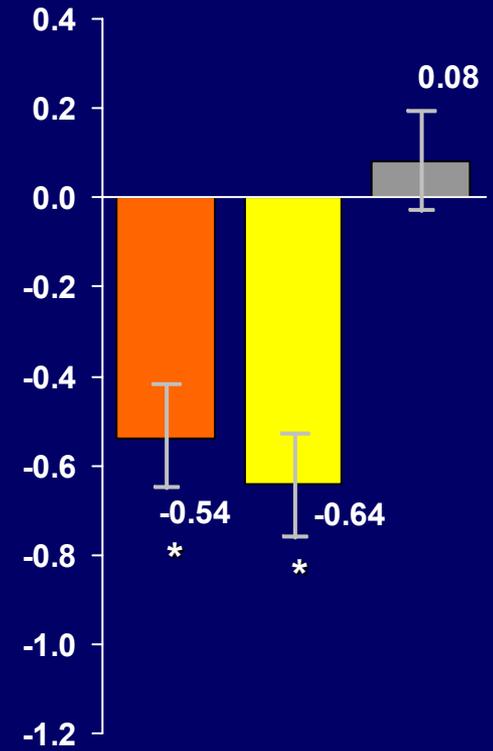
| Dose         | SAXA + MET |      |      | PBO + MET | SAXA + TZD |      | PBO + TZD | SAXA + GLY |      | PBO + GLY |
|--------------|------------|------|------|-----------|------------|------|-----------|------------|------|-----------|
|              | 2.5        | 5    | 10   |           | 2.5        | 5    |           | 2.5        | 5    |           |
| n =          | 186        | 186  | 180  | 175       | 192        | 183  | 180       | 246        | 250  | 264       |
| Bsl Mean (%) | 8.08       | 8.07 | 7.98 | 8.06      | 8.25       | 8.35 | 8.19      | 8.36       | 8.48 | 8.44      |



\* p < .0001 vs. PBO + MET



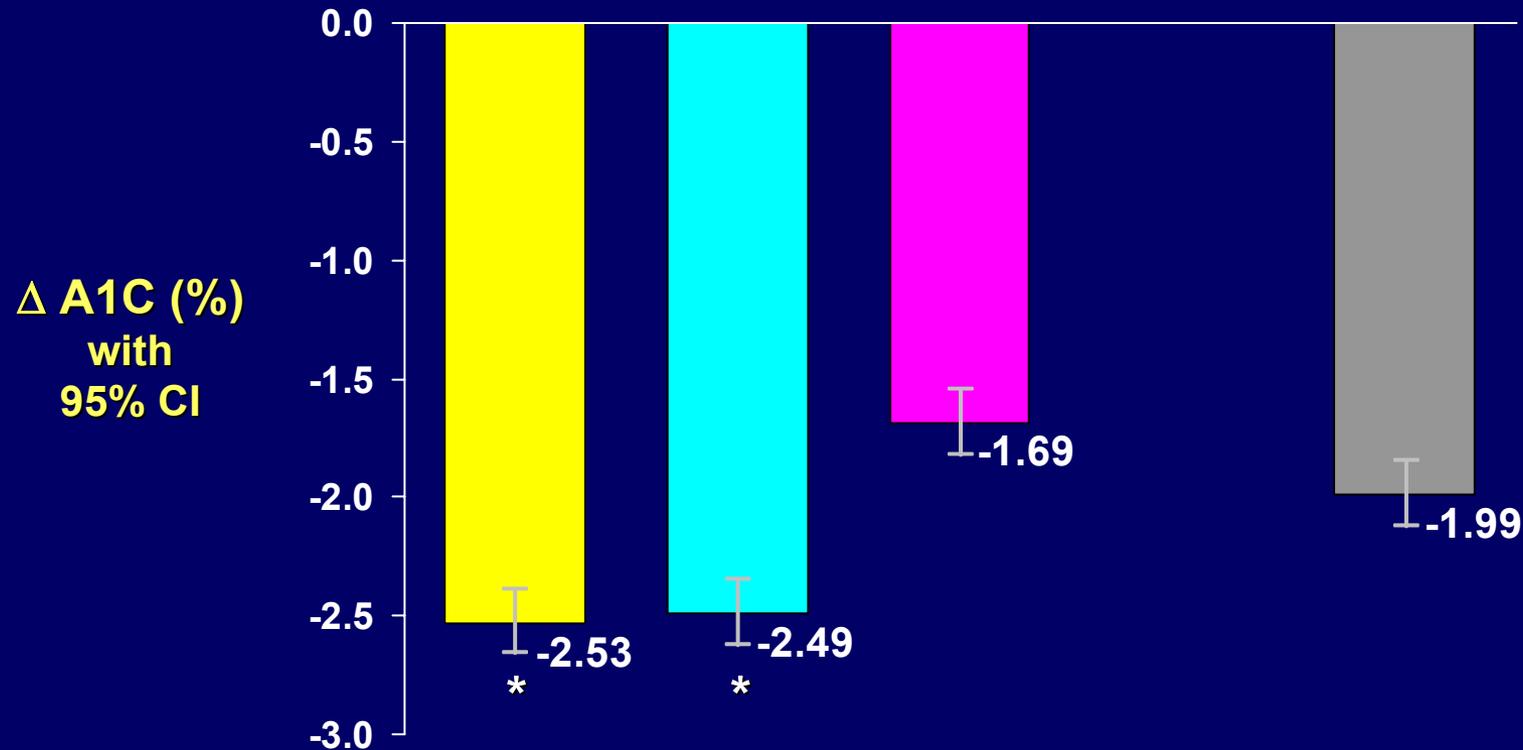
\*p < .0001 vs. PBO + TZD  
\*\* p = .0007 vs. PBO + TZD



\* p < .0001 vs. PBO + GLY

# Change from Baseline in A1C at Week 24 (LOCF)

| Dose              | SAXA (mg) + MET |      | SAXA (mg) | MET  |
|-------------------|-----------------|------|-----------|------|
|                   | 5               | 10   | 10        |      |
| n =               | 306             | 315  | 317       | 313  |
| Baseline Mean (%) | 9.41            | 9.53 | 9.61      | 9.43 |

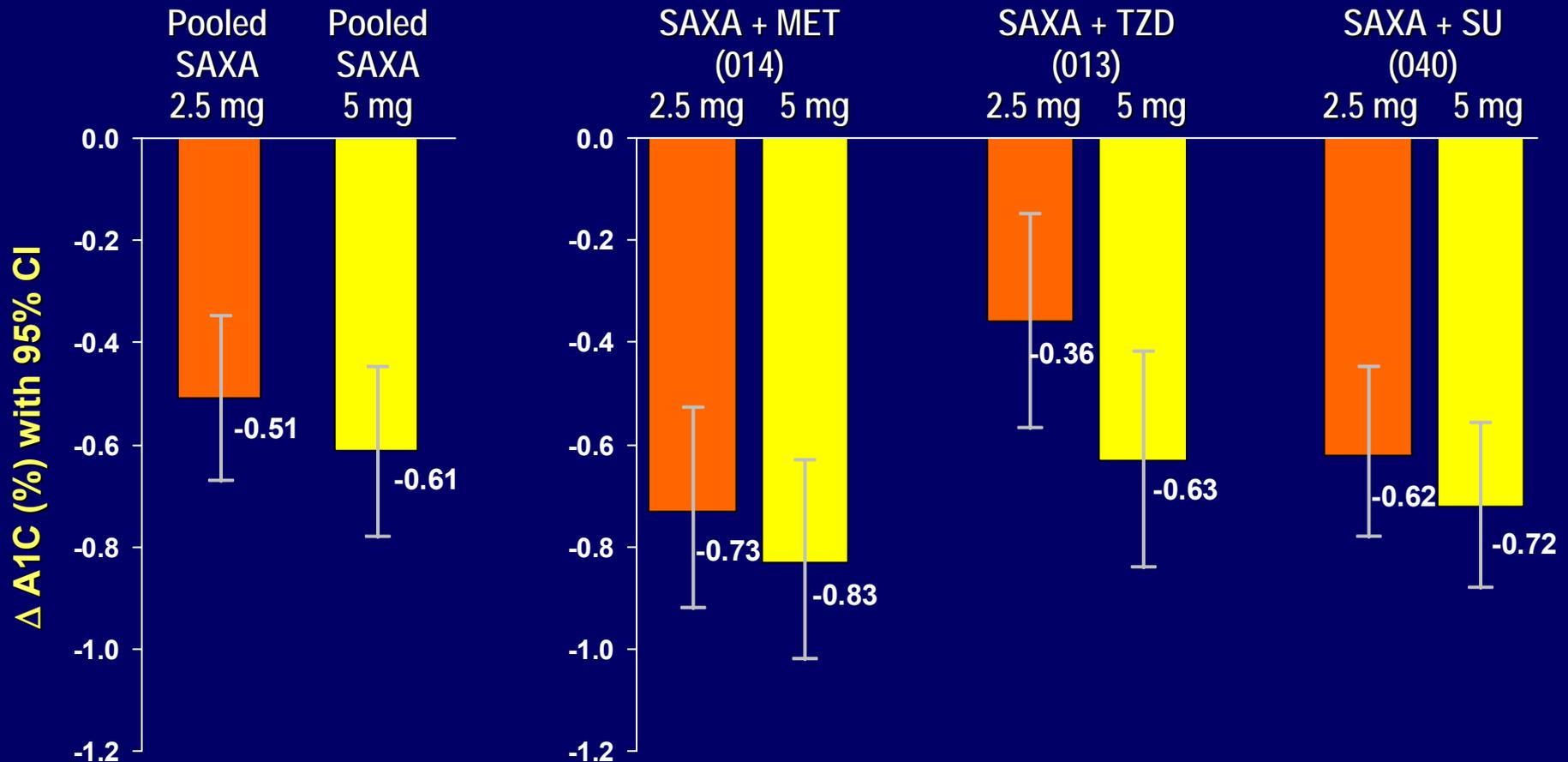


\* p < .0001 vs. MET

# Difference from Placebo in Adjusted Mean Change from Baseline in A1C

Phase 2b/3 Monotherapy Studies  
Post-hoc Pooled Analysis (Wk 12)

Phase 3 Add-on Combination Studies  
ST Period (Wk 24)

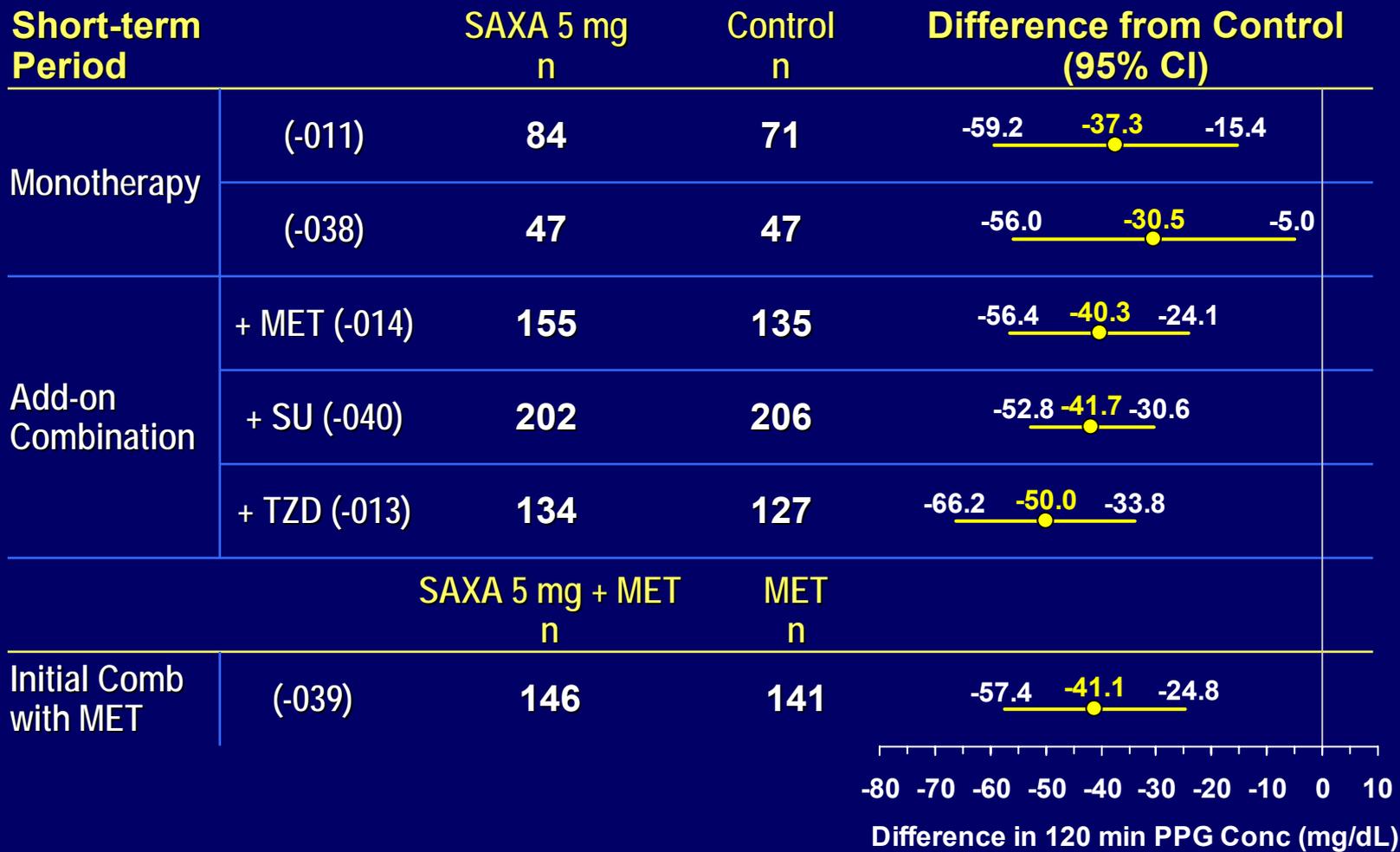


# Saxagliptin 5 mg as Recommended Usual Clinical Dose

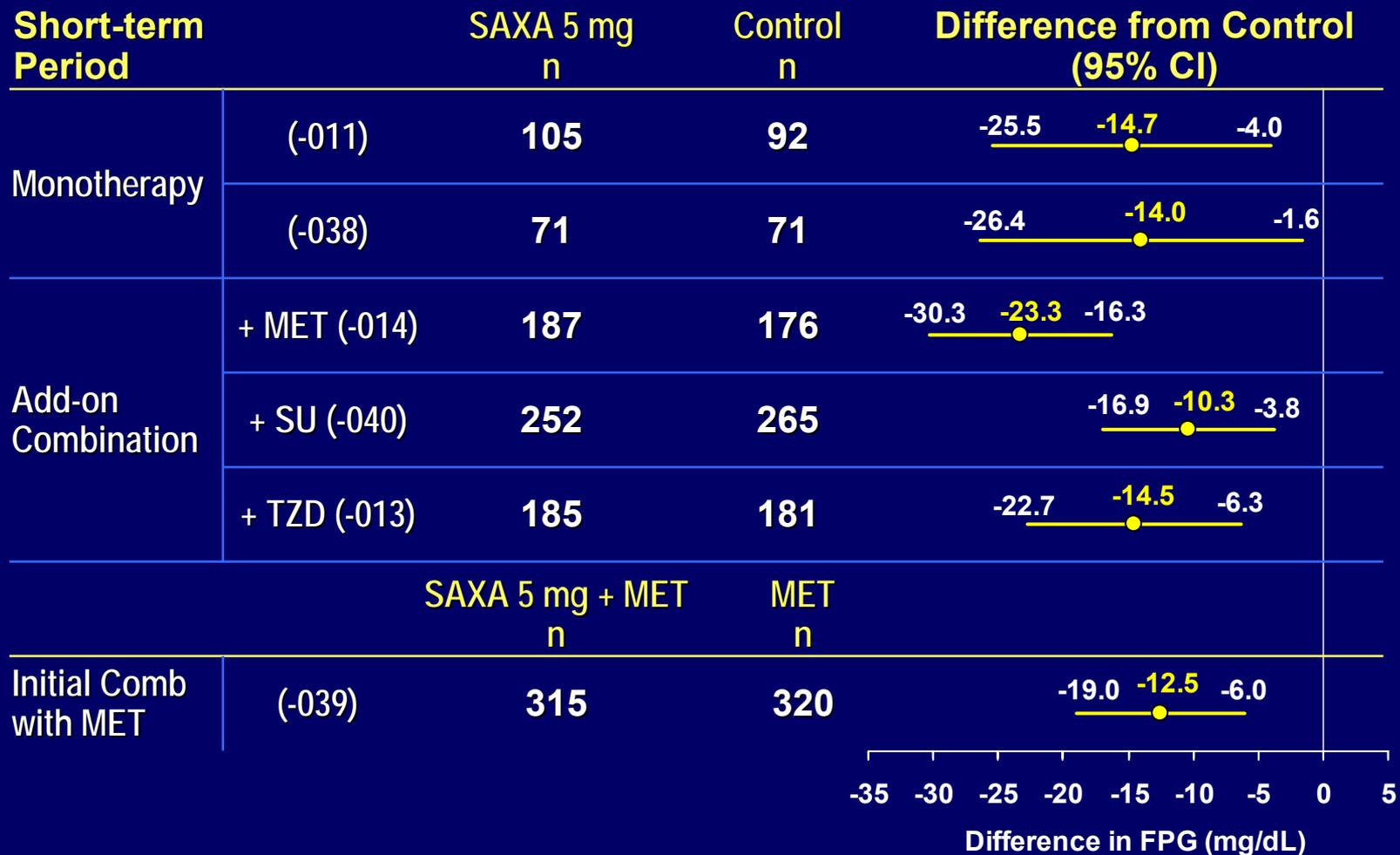
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- ◆ **Consistent efficacy benefit observed for saxagliptin 5 mg versus 2.5 mg as monotherapy, and add-on treatment (MET, TZD, SU)**
  - **Results consistent with observations of greater DPP4 inhibition at trough with 5 mg versus 2.5 mg dose**
- ◆ **No evidence for incremental efficacy benefit for 10 mg versus 5 mg dose in key glycemic parameters**
- ◆ **Given the comparable safety profile of the 2.5 and 5 mg doses, saxagliptin 5 mg is the proposed usual clinical dose**

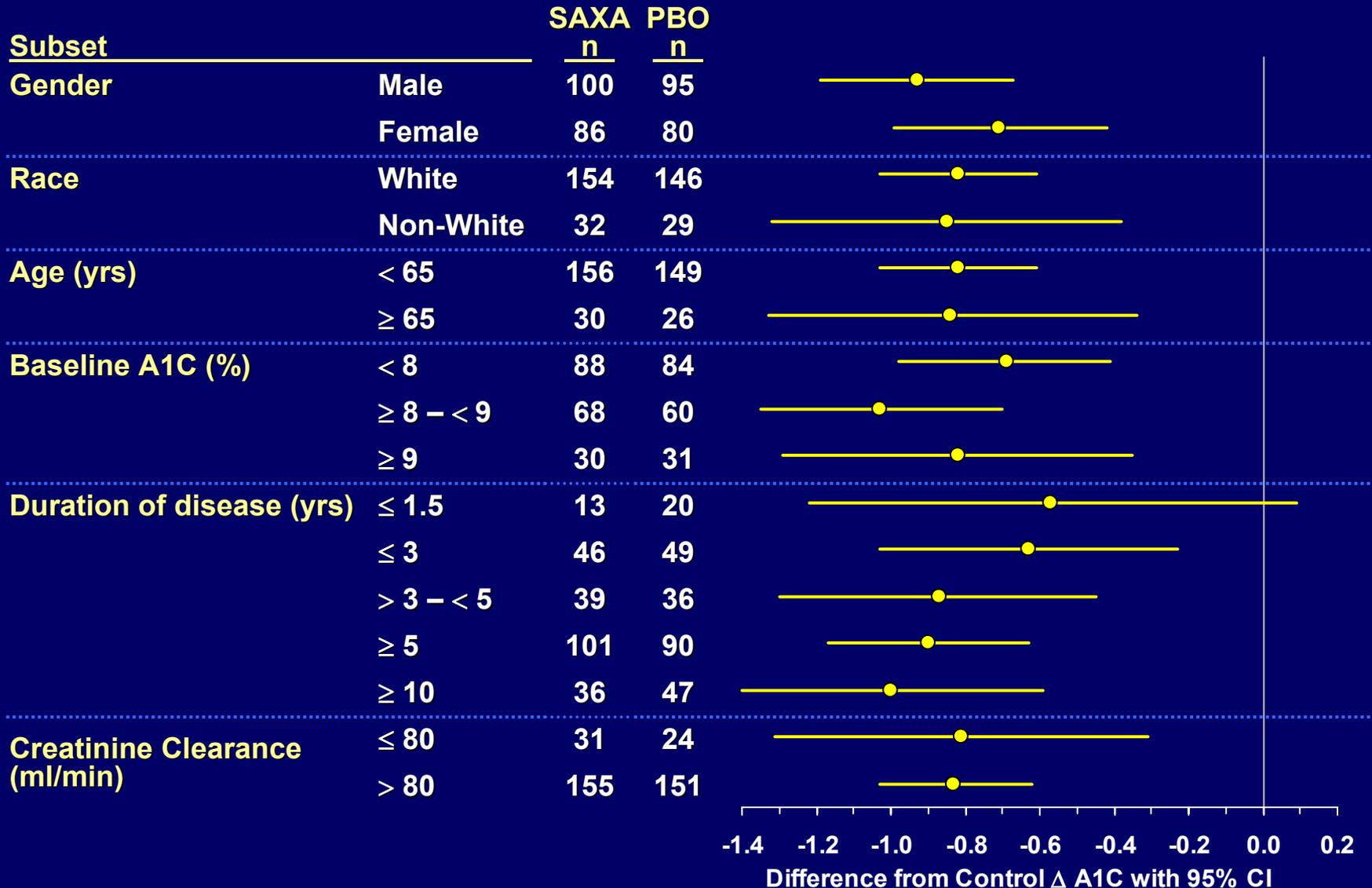
# Adjusted Mean Change from Baseline in 120 Minute PPG Concentration for Saxagliptin 5 mg (LOCF)



# Adjusted Mean Change from Baseline in FPG for Saxagliptin 5 mg (LOCF)



# Difference from Control in Change from Baseline in A1C at Week 24 (LOCF) for Saxagliptin 5 mg by Subgroup



# Summary of Efficacy

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- ◆ **Saxagliptin 5 mg provides consistent, clinically meaningful and statistically significant reductions in A1C, FPG, and PPG, together with increases in achievement of treatment targets**
- ◆ **Beneficial effect demonstrated across subgroups of demographic and baseline diabetes characteristics**

# Saxagliptin Clinical Safety

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# Saxagliptin Clinical Development Program: High Dose Exposure in Phase 1–3

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- ◆ High dose experience to provide clinical safety margin for recommended usual clinical dose of 5 mg including:
  - 400 mg QD (80x) for 2 weeks (Phase 1)
  - 100 mg QD (20x) for 6 weeks (Phase 2b)
  - 40 mg and 20 mg QD (8x) for 12 weeks (Phase 2b)
  - 10 mg QD (2x) for 102 weeks (Phase 3)
- ◆ Studied 3 doses in Phase 3 (2.5 mg, 5 mg, 10 mg QD)
  - Approximately one-third of experience accrued at highest dose evaluated (10 mg)

# FDA Guidance for Exposure in Phase 2b/3 and Extent of Exposure to Saxagliptin

| <b>Exposure</b>                | <b>ICH<sup>4</sup><br/>Guidance</b> | <b>FDA<sup>5</sup><br/>Guidance</b> | <b>Saxagliptin<br/>NDA</b> | <b>Saxagliptin<br/>Day 120 Update<br/>of Clinical Safety</b> |
|--------------------------------|-------------------------------------|-------------------------------------|----------------------------|--|
| <b>Total</b>                   | <b>1500</b>                         | <b>2500</b>                         | <b>3422</b>                | <b>3422</b>  |
| <b>≥ 1 Year<sup>1</sup></b>    | <b>100</b>                          | <b>1300 - 1500</b>                  | <b>1364</b>                | <b>2236</b>  |
| <b>≥ 18 Months<sup>2</sup></b> | <b>N/A</b>                          | <b>300 - 500</b>                    | <b>608</b>                 | <b>1014</b>  |
| <b>≥ 2 Years<sup>3</sup></b>   | <b>N/A</b>                          | <b>N/A</b>                          | <b>266</b>                 | <b>471</b>   |

<sup>1</sup> ≥ 50 weeks

<sup>2</sup> ≥ 76 weeks

<sup>3</sup> ≥ 102 weeks

<sup>4</sup> ICH Guidance, Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions, March 1995.

<sup>5</sup> FDA Draft Guidance for Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, February 2008.

# Saxagliptin Safety Monitoring

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- ◆ **Supplemental data collection for events of special interest**
  - **Skin lesions**
  - **Selected infections**
  - **Decreased lymphocyte or platelet counts**
  - **Localized edema**
- ◆ **Safety monitoring by independent Data Monitoring Committee**
  - **Formed at start of Phase 3 with continued monitoring to present**

# Safety Data – Populations and Datasets

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## Populations

- ◆ Study-level comparisons
- ◆ Placebo-controlled pooled population (5-study pool)
  - Two monotherapy / Add-on MET, TZD, SU
- ◆ Phase 2b/3 pooled population (8-study pool)
  - 5-study pool plus Phase 2b, Initial Combination MET, and MOA studies

## Study Period Analyzed

- ◆ Short-term (24-week) excluding rescue therapy (RT)
- ◆ Short-term (24-week) including rescue therapy
- ◆ Short-term and Long-term including rescue therapy

# Demographic and Baseline Characteristics

|  |                    | Saxa 2.5 mg<br>N = 937 | Saxa 5 mg<br>N = 1269 | Saxa 10 mg<br>N = 1000 | All Saxa <sup>(a)</sup><br>N = 3356 | Control <sup>(b)</sup><br>N = 1251 |
|--|--------------------|------------------------|-----------------------|------------------------|-------------------------------------|------------------------------------|
| <b>Age</b>   | Mean (SD) years    | 54.6 (10.0)            | 53.7 (10.3)           | 52.7 (10.7)            | 53.6 (10.3)                         | 53.9 (10.6)                        |
| <b>Race</b>  | White, n (%)       | 650 (69)               | 902 (71)              | 775 (78)               | 2456 (73)                           | 889 (71)                           |
|  | Non-white, n (%)   | 287 (31)               | 367 (29)              | 225 (23)               | 900 (27)                            | 362 (29)                           |
| <b>Gender</b>  | Male, n (%)        | 444 (47)               | 625 (49)              | 495 (50)               | 1659 (49)                           | 620 (50)                           |
|  | Female, n (%)      | 493 (53)               | 644 (51)              | 505 (51)               | 1697 (51)                           | 631 (50)                           |
| <b>Duration of T2DM</b>  |                    |                        |                       |                        |                                     |                                    |
|  | Mean (SD) years    | 5.1 (5.2)              | 4.1 (5.1)             | 2.5 (3.6)              | 3.8 (4.8)                           | 4.1 (5.0)                          |
|  | ≥ 5 years, n (%)   | 386 (41)               | 400 (32)              | 193 (19)               | 1005 (30)                           | 388 (31)                           |
|  | ≥ 10 years, n (%)  | 150 (16)               | 145 (11)              | 53 (5)                 | 356 (11)                            | 151 (12)                           |
| <b>A1C</b>   | Mean (SD) %        | 8.1 (0.99)             | 8.5 (1.18)            | 9.0 (1.42)             | 8.5 (1.26)                          | 8.4 (1.23)                         |
| <b>CrCl</b>  | ≤ 80 mL/min, n (%) | 158 (17)               | 241 (19)              | 147 (15)               | 560 (17)                            | 238 (19)                           |
|  | > 80 mL/min, n (%) | 779 (83)               | 1027 (81)             | 853 (85)               | 2795 (83)                           | 1013 (81)                          |
| <b>At least one diabetes-related microvascular complication<sup>*</sup>, n (%)</b> |                    | 181 (19)               | 216 (17)              | 130 (13)               | 547 (16)                            | 219 (18)                           |

(a) Includes 20, 40 and 100 mg experience from CV181008

(b) Includes metformin monotherapy from CV181039

\* Microvascular complication includes: retinopathy, neuropathy, nephropathy, and microalbuminuria.

# Presentation of Safety Data

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- ◆ **Overall Adverse Events, Serious Adverse Events, and Discontinuations for AE**
- ◆ **Hypoglycemia**
- ◆ **Dermatologic Safety**
- ◆ **Lymphocytes**
- ◆ **General Safety Profile**
- ◆ **Cardiovascular Events**

# Overall Summary of Adverse Events

## Percent of Patients

|  | <b>SAXA<br/>2.5 mg<br/>N = 882</b> | <b>SAXA<br/>5 mg<br/>N = 882</b> | <b>SAXA<br/>10 mg<br/>N = 279</b> | <b>All SAXA<br/>N = 2043</b> | <b>PBO<br/>N = 799</b> |
|--|------------------------------------|----------------------------------|-----------------------------------|------------------------------|------------------------|
| <b>At least one AE</b>                 | <b>72.0</b>                        | <b>72.2</b>                      | <b>76.7</b>                       | <b>72.7</b>                  | <b>70.6</b>            |
| <b>Deaths</b>                          | <b>0.2</b>                         | <b>0</b>                         | <b>0</b>                          | <b>&lt;0.1</b>               | <b>0.3</b>             |
| <b>At least one SAE</b>                | <b>3.5</b>                         | <b>3.4</b>                       | <b>2.5</b>                        | <b>3.3</b>                   | <b>3.4</b>             |
| <b>Discontinuations<br/>due to AEs</b> | <b>2.2</b>                         | <b>3.3</b>                       | <b>3.9</b>                        | <b>2.9</b>                   | <b>1.8</b>             |

# Reported and Confirmed Hypoglycemia Adverse Events

| Short-term Period<br>Excludes RT         |                  | Percent            |                     | Reported<br><i>Confirmed</i> |          |      |
|--|------------------|--------------------|---------------------|------------------------------|----------|------|
|  |                  | SAXA<br>2.5 mg     | SAXA<br>5 mg        | SAXA<br>10 mg                | All SAXA | PBO  |
| Pooled Monotherapy<br>(-011, -038)       | Reported         | 4.0                | 5.6                 | 8.2                          | 5.4      | 4.1  |
|  | <i>Confirmed</i> | 0                  | 0                   | 0                            | 0        | 0    |
| Add-on Combination<br>+ MET (-014)       | Reported         | 7.8                | 5.2                 | 3.9                          | 5.7      | 5.0  |
|  | <i>Confirmed</i> | 0.5                | 0.5                 | 0.6                          | 0.5      | 0.6  |
| + SU (-040)                              | Reported         | 13.3               | 14.6                | —                            | 14.0     | 10.1 |
|  | <i>Confirmed</i> | 2.4                | 0.8                 | —                            | 1.6      | 0.7  |
| + TZD (-013)                             | Reported         | 4.1                | 2.7                 | —                            | 3.4      | 3.8  |
|  | <i>Confirmed</i> | 0.5                | 0                   | —                            | 0.3      | 0    |
| Placebo-controlled<br>Pooled Population* | Reported         | 7.6                | 7.8                 | 5.4                          | 7.4      | 6.8  |
|  | <i>Confirmed</i> | 0.8                | 0.5                 | 0.4                          | 0.6      | 0.4  |
|  |                  | SAXA 5 mg<br>+ MET | SAXA 10 mg<br>+ MET | SAXA<br>10 mg                | All SAXA | MET  |
| Initial Combination<br>with MET (-039)   | Reported         | 3.4                | 5.0                 | 1.5                          | 3.3      | 4.0  |
|  | <i>Confirmed</i> | 0                  | 0.6                 | 0                            | 0.2      | 0.3  |

\* Placebo-controlled Pooled Population includes RT.

Source: (reported) CSR Table S.6.5.6 [-039], (confirmed) Table S.8.6.1, Table S.6.5.6A [-039].

# Summary – Dermatologic Safety

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- ◆ **Multi-focal reversible skin lesions (erosions and ulcers) observed in cynomolgus monkeys exposed to saxagliptin**
- ◆ **Phase 3 safety monitoring included investigator training, supplemental data collection with special case-report forms**
- ◆ **Analyses performed based on pre-defined Medical Dictionary for Regulatory Activities (MedDRA) preferred terms similar to non-clinical findings in monkey**
  - **Terms included skin ulcer, erosion, and necrosis**
  - **Events infrequent – none led to study drug discontinuation**
  - **None considered related to study drug**
- ◆ **Based on clinical program, no evidence observed for human clinical correlate to monkey skin findings**

# Summary – Lymphocyte Count Analyses

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- ◆ **Dose-dependent reductions in lymphocyte count seen in Phase 1 and 2b studies at higher doses**
- ◆ **In Phase 3 studies, small, dose-dependent reduction in mean absolute lymphocyte count observed with 5 and 10 mg dose**
  - **Decline with 5 mg dose approximately 100 c/ $\mu$ L relative to PBO from baseline mean lymphocyte count of approximately 2200 c/ $\mu$ L**
  - **Decreases were non-progressive with daily dosing of saxagliptin up to 128 weeks**
- ◆ **Lymphocyte decreases not associated with clinical adverse consequences**
  - **In patients with low lymphocyte counts, types of infections observed were similar to those in general population (i.e., no unusual opportunistic infections)**
  - **Comparable infection-related AE rates for saxagliptin 5 mg and placebo without signal for opportunistic events in overall population**

# General Safety Profile

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- ◆ Well-tolerated at all doses studied in Phase 3
- ◆ Low risk for hypoglycemia
- ◆ No adverse effects in lipid parameters, blood pressure or heart rate
- ◆ Associated with no or minimal differences in weight change compared with control
- ◆ No identified hepatic, pancreatic, skeletal myopathy, or renal safety signals
- ◆ No evidence for clinically meaningful effects on hematology or chemistry parameters

# Saxagliptin Cardiovascular Safety

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Robert Wolf, MD, FACC

# Chronology for Saxagliptin Program and FDA Guidance on Evaluating CV Risk

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- Jul 2005 ♦ **End of Phase 2 Meeting: FDA provided guidance to Sponsor on Phase 3**

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- Nov 2007 ♦ **Pre-NDA Meeting: FDA requested longer exposure in Phase 3**
  - ♦ **Sponsor delayed submission to accommodate FDA request**

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- Jun 2008 ♦ **Sponsor analyzed Acute CV Events, submitted NDA to FDA**

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- Sep 2008 ♦ **In response to a request from FDA, Sponsor defined and analyzed Major Adverse Cardiovascular Events (MACE) in the NDA database**

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- Dec 2008 ♦ **Sponsor updated analyses of MACE based on Day 120 Update database**

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- Jan 2009 ♦ **FDA provided definitions and methods of analysis for MACE to Sponsor**
  - ♦ **Sponsor re-analyzed MACE as requested by FDA**

# FDA Criteria for Assessing CV Safety

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**Sponsor should compare the incidence of important CV events with the investigational agent to incidence with the control group and calculate a two-sided 95% confidence interval (95% CI) for the estimated risk ratio. Pre-marketing data showing:**

- ◆ Upper bound of 95% CI between 1.3 and 1.8 would support approval; post-marketing trial needed to show upper bound is  $<1.3$**
- ◆ Upper bound of 95% CI  $<1.3$  would support approval; post-marketing CV trial may not be necessary**
- ◆ Point estimate of 1.5 would not be reassuring even if upper bound of 95% CI is  $<1.8$**

# Application of FDA Guidance on Evaluating CV Risk to Saxagliptin Program

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- ◆ **Sponsor analyzed Acute CV Events prior to submission of NDA**
- ◆ **Sponsor retrospectively applied FDA Guidance on Evaluating CV Risk to clinical data for saxagliptin by:**
  - **Assessing multiple endpoints for CV events**
  - **Utilizing multiple analytic methods**
- ◆ **Intent of multiple endpoints and multiple analytic methods was to assess consistency of results**
- ◆ **Used endpoints and analytic methods defined by**
  - **Sponsor**
  - **FDA**

# Context for Assessment of CV Safety in Phase 2b/3

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## For Saxagliptin

- ◆ No microscopic evidence of cardiotoxicity in any nonclinical species
- ◆ No indication of adverse cardiovascular effects based on *in vitro* (hERG, Purkinje) or *in vivo* (ECG, hemodynamic) assessments in rat, dog, or monkey
- ◆ No adverse effect on lipid parameters, blood pressure, heart rate, or QTc in Phase I studies

## For another member of DPP4 inhibitor class

- ◆ No meaningful differences between groups in incidence rates of cardiac-related or ischemia-related adverse experiences<sup>1</sup>

# Cardiovascular Events in Saxagliptin Clinical Program

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## Methods

# Dataset Descriptions

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- ◆ **Population – Pool of all controlled Phase 2b/3 saxagliptin studies**
  - 4,607 subjects; 3,356 on saxagliptin
- ◆ **Dataset**
  - Short-term plus long-term experience inclusive of rescue (Day 120 Safety Update Database)
  - 5,051 pt-yrs of exposure; 3,758 pt-yrs on saxagliptin

# Assessment of Risk Ratios

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All pooled analyses stratified by study

- ◆ Incidence Rate Ratio by Mantel-Haenszel
- ◆ Incidence Ratio (ratio of proportions of patients with CV Events)
- ◆ Cox Hazard Ratio

# Major Endpoints for Assessment of CV Safety

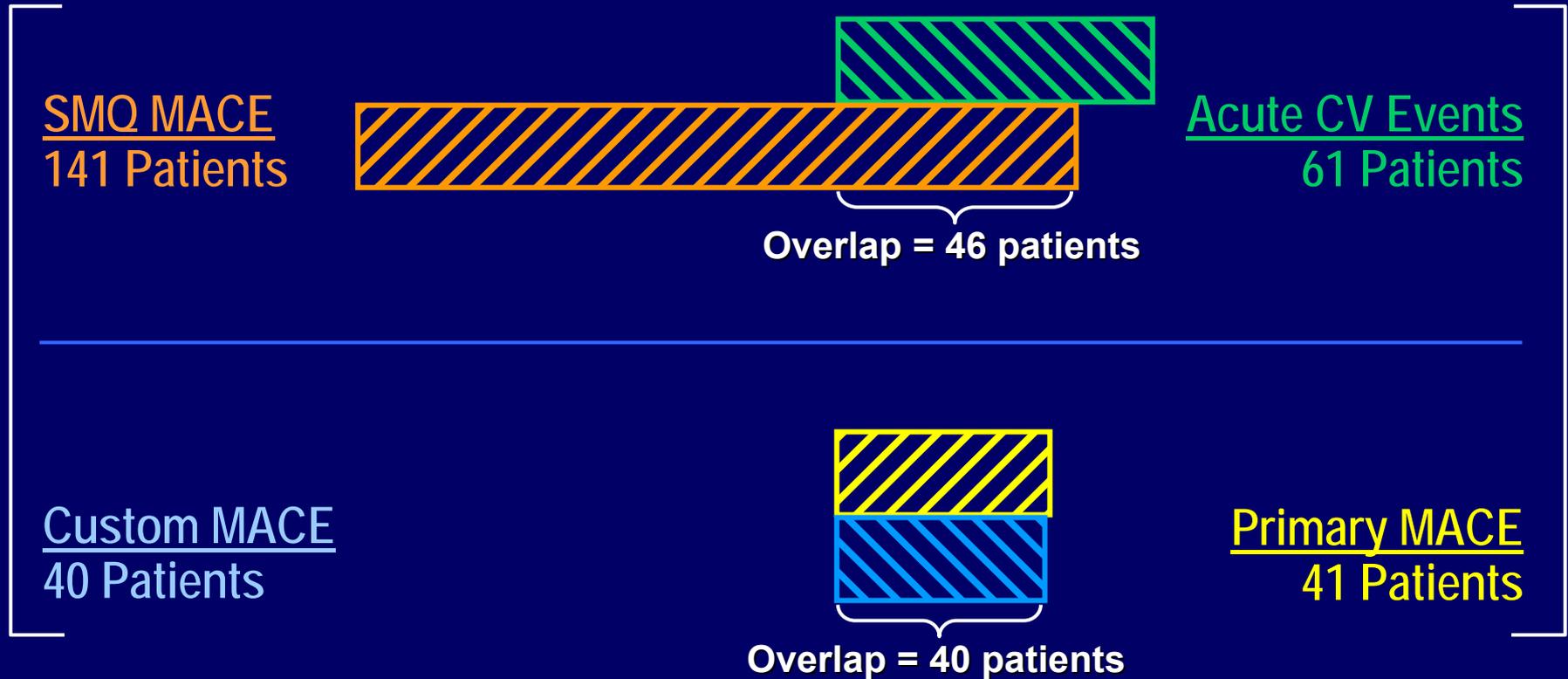
| CV Endpoint                       | Clinical Components                                 | Methods for Identification |                               | Number of Patients with Event |
|-----------------------------------|---|----------------------------|-------------------------------|-------------------------------|
|                                   |   | Number of Preferred Terms  | Clinical Review of all Deaths |                               |
| Acute CV Events (Sponsor-defined) | Acute Ischemic Events (Reversible and Irreversible) | 117                        | No                            | 61                            |
| Primary MACE (Sponsor-defined)    | CV Death, Non-fatal MI, Non-fatal Stroke            | 54                         | Yes                           | 41                            |
| Custom MACE (FDA-defined)         | CV Death, Non-fatal MI, Non-fatal Stroke            | 33                         | Yes                           | 40                            |
| SMQ MACE (FDA-defined)            | CV Death, Non-fatal MI, Non-fatal Stroke            | 148                        | Yes                           | 141                           |

MACE = Major Adverse Cardiovascular Events

# Relationship of Populations with Major CV Endpoints

FDA-defined

Sponsor-defined



# Cardiovascular Events in Saxagliptin Clinical Program

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## Results

# Cardiovascular Risk Factors (in addition to T2DM)

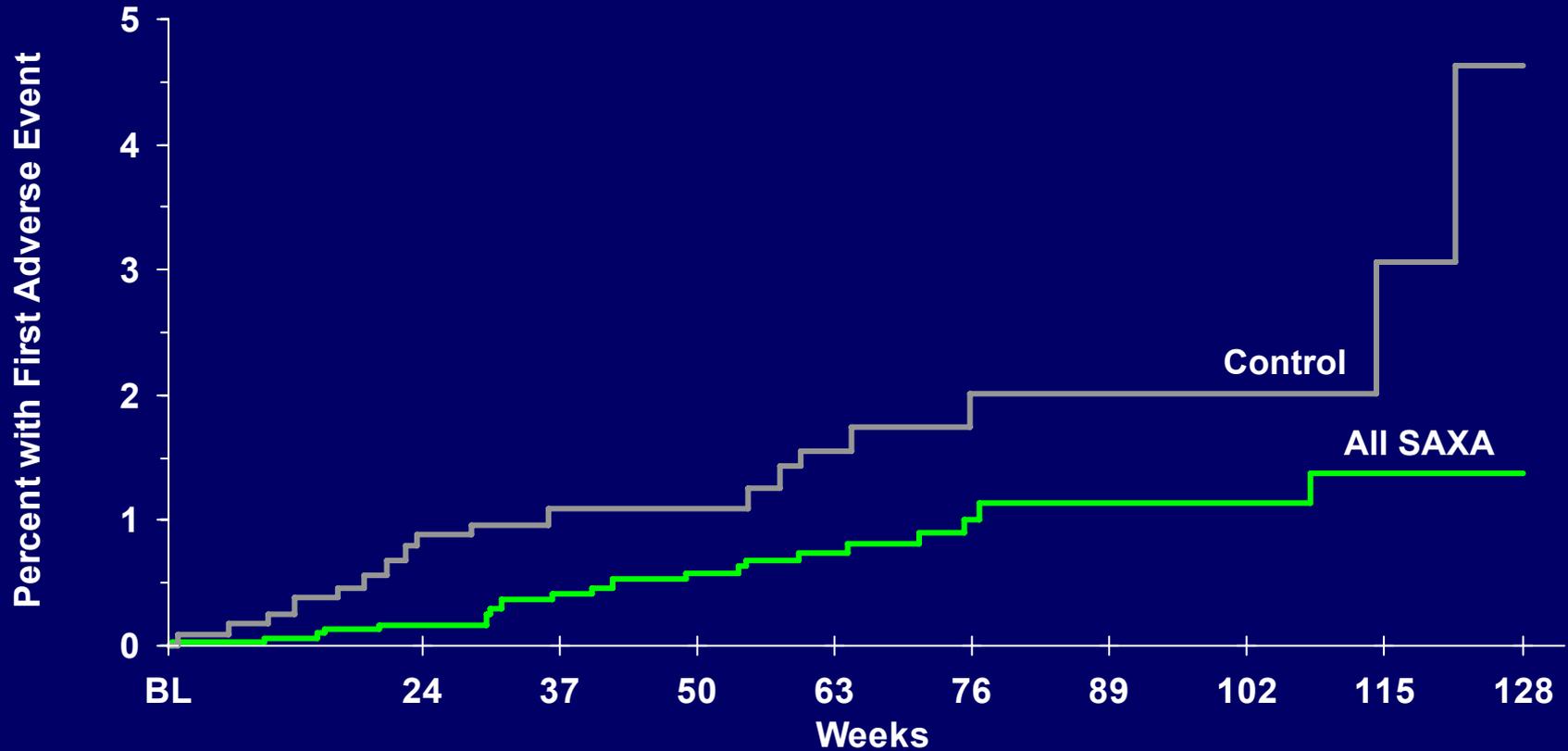
|  | Number (%) of Patients    |                          |                           |                                   |                     |
|--|---------------------------|--------------------------|---------------------------|-----------------------------------|---------------------|
|  | SAXA<br>2.5 mg<br>N = 937 | SAXA<br>5 mg<br>N = 1269 | SAXA<br>10 mg<br>N = 1000 | All SAXA <sup>3</sup><br>N = 3356 | Control<br>N = 1251 |
| <b>Patients with at least one CV Risk Factor in addition to T2DM</b> | 777 (83)                  | 1015 (80)                | 803 (80)                  | 2724 (81)                         | 1035 (83)           |
| Hypertension   | 519 (55)                  | 655 (52)                 | 510 (51)                  | 1750 (52)                         | 688 (55)            |
| Hypercholesterolemia <sup>1</sup>                                    | 471 (50)                  | 565 (45)                 | 353 (35)                  | 1475 (44)                         | 566 (45)            |
| Smoking History  | 383 (41)                  | 449 (35)                 | 393 (39)                  | 1301 (39)                         | 471 (38)            |
| First degree family member with Premature Coronary Heart Disease     | 190 (20)                  | 248 (20)                 | 186 (19)                  | 677 (20)                          | 265 (21)            |
| <b>Patients with Prior CV Disease<sup>2</sup></b>                    | 118 (13)                  | 150 (12)                 | 118 (12)                  | 404 (12)                          | 165 (13)            |

<sup>1</sup> Includes mixed dyslipidemia

<sup>2</sup> Prior CV Disease defined as previous myocardial infarction, congestive heart failure, hospitalization for unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, cerebrovascular disease, peripheral vascular disease

<sup>3</sup> Includes contribution from 20–100 mg saxagliptin in Phase 2b Study (-008).

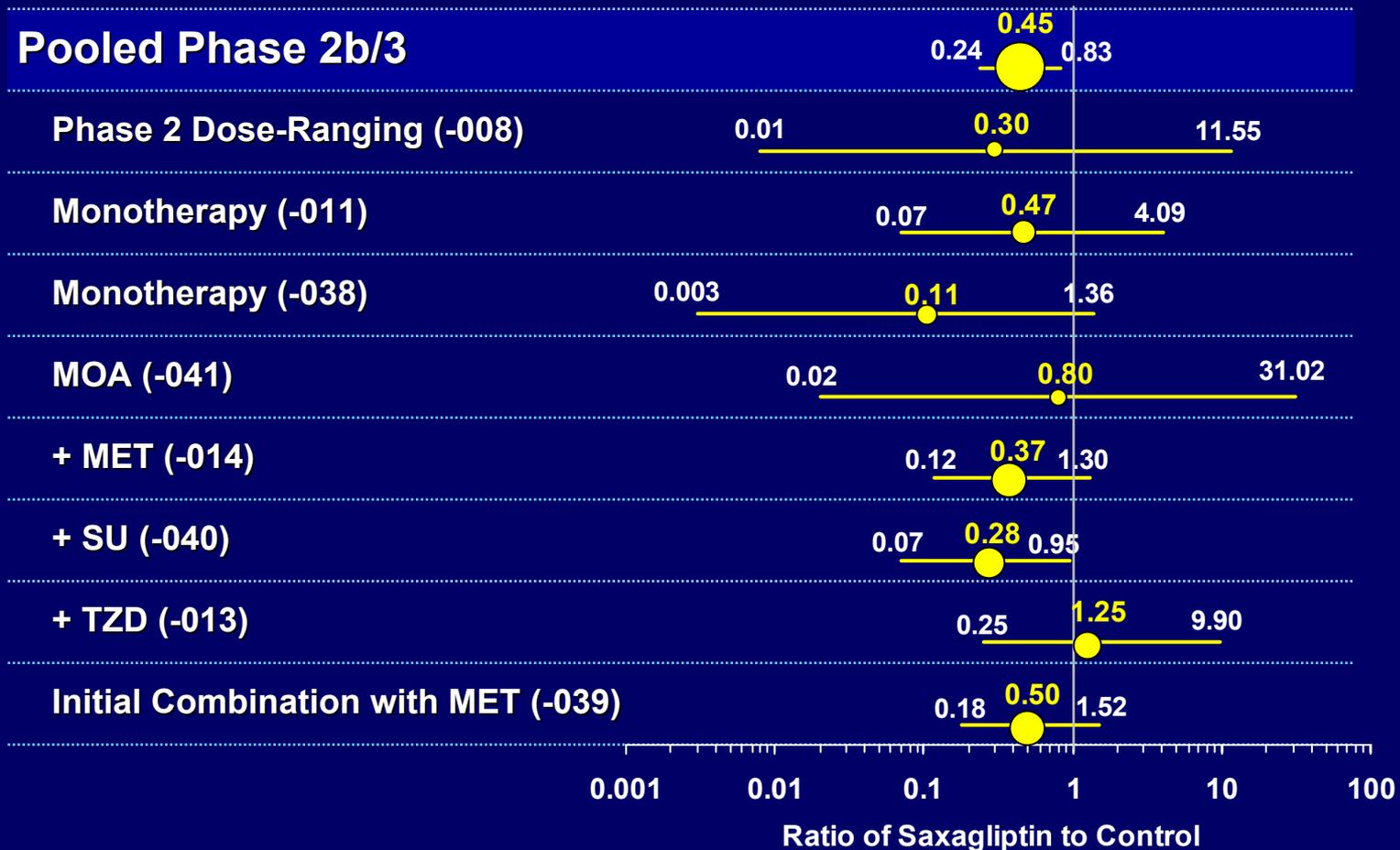
# Time to Onset of First Primary MACE



## Patients at Risk

|          |      |      |      |      |      |     |     |     |     |     |
|----------|------|------|------|------|------|-----|-----|-----|-----|-----|
| Control  | 1251 | 935  | 860  | 774  | 545  | 288 | 144 | 123 | 102 | 57  |
| All SAXA | 3356 | 2615 | 2419 | 2209 | 1638 | 994 | 498 | 436 | 373 | 197 |

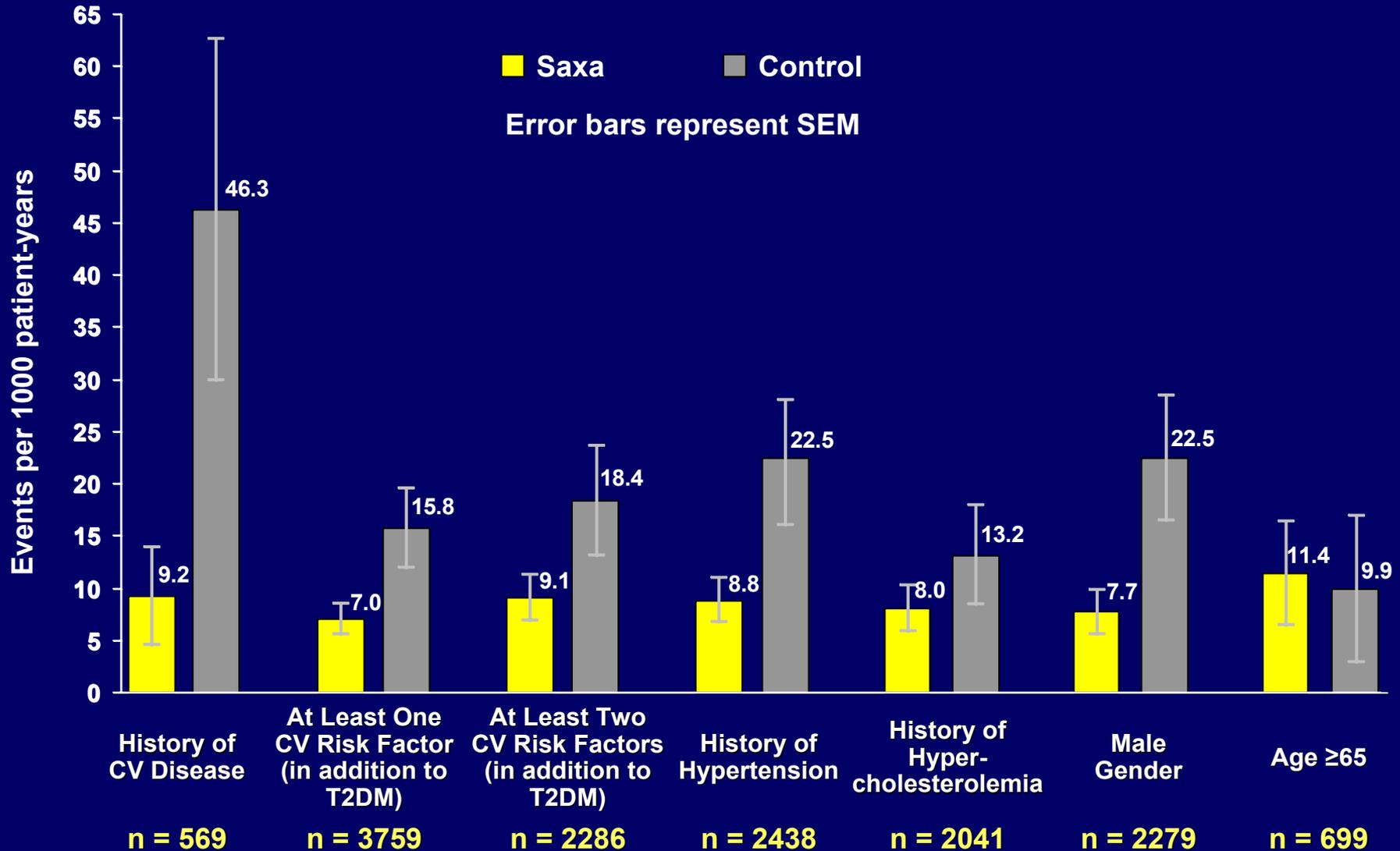
# Incidence Rate Ratio of Sponsor-defined Primary MACE



Data represent point estimate and 95% CI.  
 Size of point estimate is relative to number of events.

← Saxagliptin Better | Control Better →

# Incidence Rate for Primary MACE by Subgroups



# Frequency of Major CV Endpoints

|                                  | SAXA 2.5 mg       | SAXA 5 mg | SAXA 10 mg | All SAXA* | Control  |
|----------------------------------|-------------------|-----------|------------|-----------|----------|
| N (total patients)               | 937               | 1269      | 1000       | 3356      | 1251     |
| Total Pt-years                   | 1149              | 1462      | 1119       | 3758      | 1293     |
| Mean Duration of Follow Up (yrs) | 1.23              | 1.15      | 1.12       | 1.12      | 1.03     |
|                                  | <b>Number (%)</b> |           |            |           |          |
| <b>FDA-defined</b>               |                   |           |            |           |          |
| SMQ MACE                         | 28 (3.0)          | 37 (2.9)  | 30 (3.0)   | 100 (3.0) | 41 (3.3) |
| Custom MACE                      | 6 (0.6)           | 6 (0.5)   | 11 (1.1)   | 23 (0.7)  | 17 (1.4) |
| <b>Sponsor-defined</b>           |                   |           |            |           |          |
| Primary MACE                     | 6 (0.6)           | 6 (0.5)   | 11 (1.1)   | 23 (0.7)  | 18 (1.4) |
| Acute CV Events                  | 14 (1.5)          | 10 (0.8)  | 14 (1.4)   | 38 (1.1)  | 23 (1.8) |

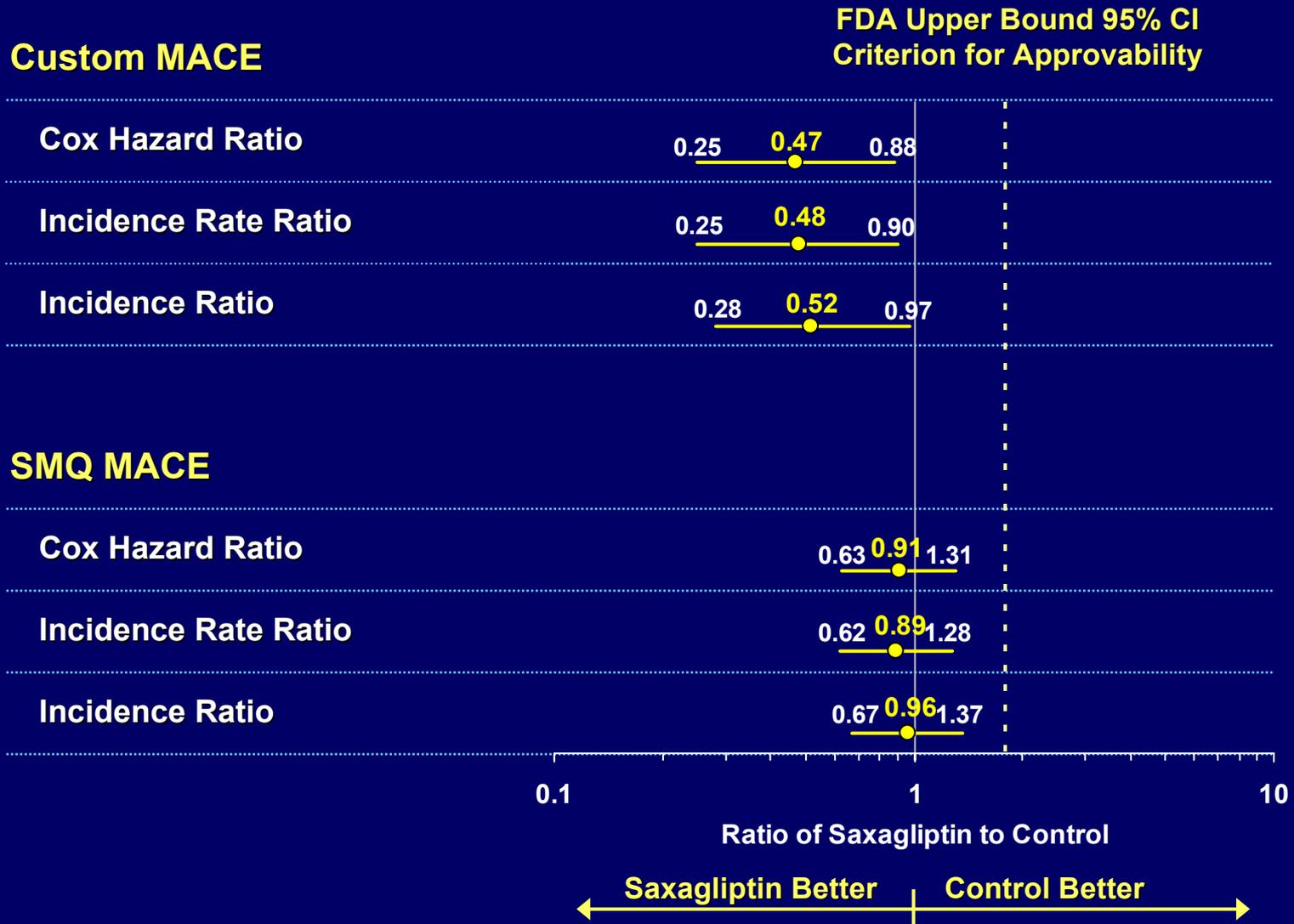
\* Includes contribution from 20–100 mg saxagliptin in Phase 2b Study (-008).

# Frequency of Additional CV Endpoints

|  | SAXA 2.5 mg       | SAXA 5 mg | SAXA 10 mg | All SAXA* | Control  |
|--|-------------------|-----------|------------|-----------|----------|
| N (total patients)                           | 937               | 1269      | 1000       | 3356      | 1251     |
| Total Pt-years                               | 1149              | 1462      | 1119       | 3758      | 1293     |
| Mean Duration of Follow Up (yrs)             | 1.23              | 1.15      | 1.12       | 1.12      | 1.03     |
|  | <b>Number (%)</b> |           |            |           |          |
| Patients with <i>Any</i> Cardiac Disorder AE | 53 (5.7)          | 63 (5.0)  | 48 (4.8)   | 164 (4.9) | 71 (5.7) |
| <b>FDA-defined</b>                           |                   |           |            |           |          |
| Ischemic Heart Disease                       | 14 (1.5)          | 17 (1.3)  | 12 (1.2)   | 43 (1.3)  | 24 (1.9) |
| Cardiac Failure                              | 8 (0.9)           | 7 (0.6)   | 5 (0.5)    | 20 (0.6)  | 7 (0.6)  |
| Cardiac Arrhythmias                          | 32 (3.4)          | 36 (2.8)  | 31 (3.1)   | 99 (2.9)  | 37 (3.0) |
| Other  | 9 (1.0)           | 8 (0.6)   | 6 (0.6)    | 23 (0.7)  | 7 (0.6)  |
| <b>Sponsor-defined</b>                       |                   |           |            |           |          |
| Secondary MACE                               | 8 (0.9)           | 7 (0.6)   | 11 (1.1)   | 26 (0.8)  | 20 (1.6) |
| All Death                                    | 3 (0.3)           | 3 (0.2)   | 4 (0.4)    | 10 (0.3)  | 12 (1.0) |
| CV Death                                     | 1 (0.1)           | 2 (0.2)   | 4 (0.4)    | 7 (0.2)   | 10 (0.8) |

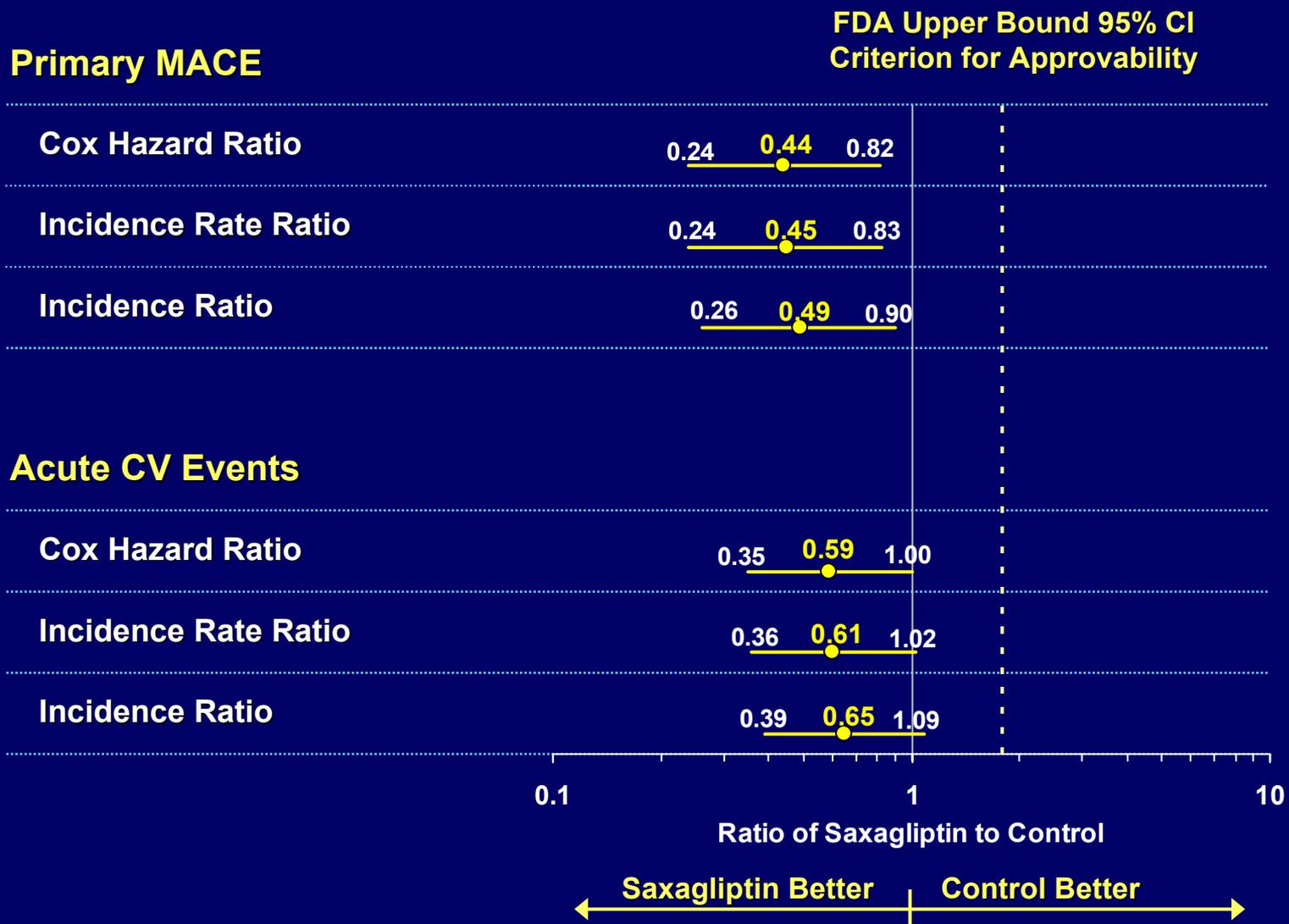
\* Includes contribution from 20–100 mg saxagliptin in Phase 2b Study (-008).

# Stratified Analyses of FDA-defined MACE



Data represent point estimate and 95% CI.

# Stratified Analyses of Sponsor-defined Primary MACE and Acute CV Events



Data represent point estimate and 95% CI.

# Cardiovascular Safety Summary and Conclusions

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- ◆ Analyzed multiple CV endpoints using multiple analytic techniques to assess consistency of results
- ◆ Analyzed CV endpoints in Phase 2b/3 Pooled Populations by subgroup and by study

**Results are consistent with FDA criteria for excluding an unacceptable CV risk.**

# Saxagliptin Benefit-Risk

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# Continued Unmet Need in Treatment of Type 2 Diabetes

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- ◆ **Increasing global prevalence of Type 2 diabetes**
- ◆ **Patients not at treatment goals or targets**
- ◆ **Progression of disease frequently leads to failure with initial monotherapy, requiring earlier combination therapy**
  - **Need to target multiple underlying defects**
- ◆ **Safety and tolerability concerns in existing agents**

# Saxagliptin – Demonstrated Benefits

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## Clinically meaningful reductions in A1C, FPG, and PPG

- ◆ **Demonstrated in wide-range of treatment contexts (monotherapy, add-on and initial combination)**
- ◆ **Consistent effect across subgroups**
- ◆ **Complementary mechanism of action to currently existing therapies**

# Saxagliptin – Favorable Safety Profile

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- ◆ Studied in extensive clinical program at exposures up to 80x proposed usual clinical dose
- ◆ Well-tolerated at all doses studied in Phase 3
- ◆ Low risk for hypoglycemia
- ◆ No or minimal differences in body weight change compared with control
- ◆ No identified hepatic, pancreatic, renal safety signals
- ◆ No human clinical correlate to monkey skin-findings
- ◆ Small decrease in mean, absolute lymphocyte count
  - Not associated with effect on infectious-related AEs
  - Changes stable, non-progressive over long-term dosing

# Saxagliptin – CV Safety Profile

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- ◆ Studied extensively in large, comprehensive Phase 2b/3 program with repeated dosing to 2.5 years
- ◆ No identified CV safety signal

# Conclusion

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- ◆ **Saxagliptin provides meaningful benefits in glycemic control**
- ◆ **Saxagliptin provides a favorable safety and tolerability profile**
- ◆ **Saxagliptin offers a new treatment option with a favorable benefit / risk profile for patients with Type 2 diabetes**

# Assessment of Saxagliptin Post-Approval

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**Brian Daniels, MD**

# Assessment of Saxagliptin Post-Approval: Pharmacovigilance and Observational Studies

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- ◆ **Post-marketing Pharmacovigilance Practices**
  - Spontaneous reports with additional targeted questionnaires
  - Analysis of FDA AERS database as needed
- ◆ **Pharmacoepidemiology studies**
  - Utilizing large US and EU databases
  - Comparing saxagliptin with oral anti-diabetic agents

# Assessment of Saxagliptin Post-Approval: Randomized Data

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- ◆ **Phase 3b and Phase 4 clinical trials with independent adjudication of CV events**
- ◆ **Sponsor is planning a large, randomized, event-driven, controlled trial that will:**
  - **characterize long-term benefit of saxagliptin in the management of diabetes**
  - **further develop the CV profile using prospective adjudication and analysis**
  - **study a population at an elevated risk for CV events**
  - **provide another mechanism for the continued assessment of the clinical profile of saxagliptin**